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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	P	ATTORNEY DOCKET NO.
09/425,075	10/21/99	CHOUDARY		

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EXAMINER	
HELMS, A.	
ART UNIT	**PAPER NUMBER**
1642	6

DATE MAILED: 04/19/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/425,075	Choudary et al
Examiner	**Group Art Unit**
Larry R. Helms Ph.D.	1642

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-21* is/are pending in the applicat

Of the above, claim(s) *14-18* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-13 and 19-21* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 1-13 and 19-21, drawn to a method for large-scale production of an antibody in transformed yeast cells, vectors and host cell, classified in class 435, subclass 69.6.

   II. Claims 14-18, drawn to an antibody, classified in class 530, subclass 387.1.

2. The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the antibody of Group II can be made by several different methods such as immunizing an animal with an antigen or produced in P. pastoris with different cloning steps utilizing different signal sequences and different steps to confirm the intactness of the insert, such as restriction digests, for example, in addition to the method of Group I.

3. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter and different classifications, restriction for examination purposes as indicated is proper.

4. During a telephone conversation with Mr. James Coburn on March 1, 2000 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-13 and 19-21. Affirmation of this election must be made by applicant in replying to this Office action. Claims 14-18 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(I).

6. Claims 1-13 and 19-21 are under examination.

Specification

7. The disclosure is objected to because of the following informalities:

a. The title of the invention is not descriptive because it recites an antibody as well as the method for producing the antibody. A new title is required that is clearly indicative of the invention to which the claims are directed.

b. The brief description of the drawing needs to have a separate description for Figures 6A-6C.

Appropriate correction is required.

Drawings

8. The drawings are considered to be informal because they fail to comply with 37 CFR 1.84(a)(1) which requires black and white drawings using India ink or its equivalent.

a. Photographs and color drawings are acceptable only for examination purposes unless a petition filed under 37 CFR 1.84(a)(2) or (b)(1) is granted permitting their use as formal drawings. In the event applicant wishes to use the drawings currently on file as formal drawings, a petition must be filed for acceptance of the photographs or color drawings as formal drawings. Any such petition must be accompanied by the appropriate fee as set forth in 37 CFR 1.17(I), three sets of drawings or photographs, as appropriate, and, if filed under the provisions of 37 CFR 1.84(a)(2), an amendment to the first paragraph of the brief description of the drawings section of the specification which states:

> The file of this patent contains at least one drawing executed in color. Copies of this patent with color drawing(s) will be provided by the Patent and Trademark Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings have been satisfied.

b. Figure 6A-C needs to have separate views.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-13 and 19-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-13 are indefinite for reciting incomplete method claims which do not clearly include a resolution step which reads back on the preamble of the claimed method. Merely reciting method steps, detecting the presence of the recombinant antibody by Western blot and testing the antibody for binding does not result in a method of large scale production of an antibody. The claims should conclude with a step of producing the antigen-specific intact

antibody thereby producing the antibody as required by the preamble, which recites "a method for a large-scale production of antigen specific intact antibody".

b. Claims 1-13 and 20 are indefinite for reciting the term "genes" in claims 1, 7, 8, and 20. According to Genes IV (Lewin et al, Oxford University Press, page 810, 1990), a gene is defined as "the segment of DNA involved in producing a polypeptide chain; it includes regions preceding and following the coding regions (leader and trailer) as well as intervening sequences (introns) between individual coding segments (exons)." From the teachings of the specification, however, the nucleic acid sequences encoding the heavy and light chain regions of the antibody do not include expression control elements that fall under the definition of a gene. Accordingly, the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

c. Claims 1-13 and 19-21 are indefinite because they contain the abbreviation "P. pastoris" and "PCR" in claims 1, 2, 7, 10, and 11. Full terminology should be in first instance of the claims followed by the abbreviation in parentheses. Dependent claims may then use the abbreviation. Abbreviations render the claim indefinite because the same abbreviation may represent more than one element or concept.

d. Claims 1-13 are indefinite for reciting "sequence" in claims 1(e), (g), (k), and 13. The term "sequence" refers to information describing the nucleic acid or amino acid sequence. Information is not a chemical structure, therefore, it is not clear how "sequences" can be linked to

nucleic acid molecules. Replacing this term with polynucleotide, DNA, RNA or polypeptide, as appropriate, would be sufficient to obviate this rejection.

e. Claim 1 recites the limitation "said expression cassettes" in the claim. There is insufficient antecedent basis for this limitation in the claim. Is "said expression cassettes" to mean those recited in claims 1(a) or 1(c) or 1(d)?

f. Claims 1-13 are indefinite for reciting "preparing and transforming P. pastoris with BglII, NotI, SacI, SalI or Stu1-linearized recombinant plasmid" in claim 1 for the exact meaning of the phrase is not clear. It is not clear if the phrase is meant to mean that all of the recited restriction sites are to be used of if the claim is meant to recite a Markush group. In addition it is unclear what "prepared" is to encompass. Does it mean to digest the plasmid, set the vector out on the table, or some other steps? As written, it is impossible to determine the metes and bounds of the claimed invention.

g. Claims 1-13 are indefinite for reciting "the AOX1 promoter fused to a Saccharomyces cerevisiae α-mating factor signal sequence" in claim 1(e) for the exact meaning of the phrase is not clear. It is unclear how the expression cassettes, which are DNA, are to be fused to a α-mating factor signal sequence, which is a protein. The claim should recite that the DNA encodes the signal sequence. As written, it is impossible to determine the metes and bounds of the claimed invention.

h. Claims 2-13 are indefinite for reciting "cDNA in tandem....flanked by a P. pastoris signal sequence" in claim 2 for the exact meaning is not clear. It is not clear how DNA can be

flanked by a protein signal sequence. The claim should recite flanked by DNA encoding the signal sequence. As written, it is impossible to determine the metes and bounds of the claimed invention.

l. The term "large-scale production" in claims 1 and 21 is a relative term which renders the claim indefinite. The term "large-scale production" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

j. Claims 6 and 7 are indefinite for reciting the term "pPICZαLH" because other laboratories/inventors may use the same laboratory designation to refer to different plasmids.

k. Claim 19 is indefinite for reciting "cDNA copy of immunoglobulin light and heavy chain" for the exact meaning of the phrase is not clear. It is not clear how the cDNA copy can be a protein. Is the phrase meant to mean cDNA copy of DNA encoding immunoglobulin light and heavy chain proteins? As written, it is impossible to determine the metes and bounds of the claimed invention.

l. Claim 20 is indefinite for reciting "system " for the exact meaning of the term is unclear. Does the term mean a kit, a method, a vector, or something else? As written, it is impossible to determine the metes and bounds of the claimed invention.

m. Claims 1-13, 20 and 21 are indefinite for reciting "intact antibody" or "intact antibodies" in claims 1, 20, and 21 for the exact meaning of the phrase is not clear. Does the

phrases mean an intact antigen binding site, an entire antibody, etc? As written, it is impossible to determine the metes and bounds of the claimed invention.

Claim Rejections - 35 USC § 101

11. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

12. Claim 20 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claim recites "system" and it is not known what applicant is claiming. Is the "system" a process, machine, manufacture, or composition of matter?

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 19-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Eldin et al (J. of Immunological Methods 201:67-75, 2/14/97) and as evidenced by the Invitrogen 1997 catalog (published 1/97, Yeast expression pages 14-17).

a. The claims recite a recombinant P. pastoris vector containing dual expression cassettes, each carrying a cDNA copy of immunoglobulin light and heavy chain and P. pastoris transformed with DNA encoding an antibody. For this rejection, the term "system" in claim 20 is being interpreted as an expression vector and the P. pastoris yeast transformed for expression of heterologous proteins in P. pastoris and the phrases "intact antibody" or "intact antibodies" are being interpreted as an antibody or antigen binding fragment that comprises an intact antigen binding site.

b. Eldin et al teach a recombinant P. pastoris yeast expression vector (pPIC9) for expression of an antibody, which contains an intact antigen binding site, and the P. pastoris yeast transformed with the expression vector comprising cDNA encoding an immunoglobulin light and heavy chain (see page 68-69). As evidenced by the Invitrogen 1997 catalog the pPIC9 vector is a designed to contain multiple copies of the gene of interest (see page 17) thus meeting the limitations of a dual expression cassette.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 1-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horwitz et al (Proc. Natl. Acad. Sci. USA 85:8678-8682, 1988) and further in view of Cregg et al (Developments in Industrial Microbiology 29:33-41, 1988) and The Invitrogen 1997 Catalog (published 1/97, Yeast expression pages 14-17 and Master Catalog Amendment Notice for pPICZ vectors from 4/15/96) and Sambrook et al (Molecular Cloning, A Laboratory Manual Second Edition pages 1.85, 12.16-12.20, and 13.42-13.44, 1989).

a. The claims encompass a method for large-scale production of an antibody by isolating DNA for the light and heavy chain and assembling the DNA into a P. pastoris yeast expression vector and transforming S. cerevisiae with the plasmid under control of the AOX1 promoter fused to the alpha-mating factor, transforming P. pastoris with a plasmid comprising the AOX1-antibody DNA, selectively growing and screening for expression, sequencing the DNA for integrity, detecting the presence of the antibody by Western blot, and testing the antibody for antigen binding. Further embodiments are a method wherein the antibody DNA are assembled into an expression cassette comprising P. pastoris promoter AOX1 at the 5'-terminus and a P. pastoris transcription termination sequence at the 3'-terminus and wherein the expression vector is pPICZα, the AOX1-antibody DNA is inserted by homologous recombination replacement, the selection is on medium containing zeocin, the screening is by colony-immunoblotting, restriction analysis, and the DNA inserts are confirmed by nucleotide sequence analysis. For this rejection the phrase "intact antibody" in claim 1 is being interpreted as an antibody or antigen binding fragment that comprises an intact antigen binding site.

b. Horwitz et al teach a method for the production of an antibody in S. cerevisiae yeast cells with the vectors comprising cDNA encoding for an antibody, a promoter and transcription terminator, and signal sequence (see abstract and page 8679 and figure 2). The vector was constructed with molecular biology methods and the recombinants were screened using selective conditions (see page 8680). The detection of the recombinant antibody was done by Western blot (see page 8680) and antigen-antibody binding was performed (see page 8680). Horwitz et al

does not teach a recombinant host P. pastoris transformed with a vector for expression, the AOX1-P promoter, the pPICZα vector, replacement of the yeast chromosomal AOX1 with the AOX1-antibody DNA by homologous recombination, or selection on zeocin media or screening by colony-immunoblotting, restriction analysis, or nucleotide sequence analysis. These deficiencies are made up for in the teachings of Cregg et al , the Invitrogen 1997 Catalog, and Sambrook et al.

c. Cregg et al teach production of foreign proteins in Pichia pastoris with the promoter AOX1.

d. Sambrook teach basic molecular biology methods and screening colonies by colony-immunoblotting, restriction analysis, and nucleotide sequence analysis.

e. The Invitrogen 1997 Catalog teach the pPICZα vector which uses the zeocin resistant polynucleotide for selection in P. pastoris and comprises the inducible AOX1 promoter, a poly cloning site comprising EcoRI, BsmBI, BglII, and BamHI, the α-factor signal sequence, and the vector is designed for antibody expression.

f. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method for production of an antibody in P. Pastoris comprising the claimed steps with the vectors and methods of selection, screening, detection, and binding analysis in view of Horwitz et al, Cregg et al, Sambrook et al, and the 1997 Invitrogen Catalog in order to produce antibodies in P. pastoris.

g. One of ordinary skill in the art would have been motivated to produce the claimed method because Horwitz et al teach recombinant production of proteins, specifically, an antibody in S. cerevisiae in general with selection, screening, and purification and testing antigen binding. In addition, one of ordinary skill in the art would have been motivated to produce the claimed method in P. pastoris because Cregg et al teach production of heterologous proteins in P. pastoris overcomes the problems associated with producing commercially useful levels of proteins in S. cerevisiae (see page 33, introduction) and the P. pastoris is ideally suited for the production of many heterologous proteins due to the fact that (1) a detailed understanding of the growth characteristics of the organism in high-density fermentors is known, (2) the ability to place foreign DNA into the genome in a precisely controlled manner, and (3) promoters are tightly regulated and efficiently transcribed to produce proteins at high levels. (See page 40). In addition, one of ordinary skill in the art would have been motivated to produce the claimed method because the Invitrogen Catalog teach a Pichia expression vector called pPICZα which is based on homologous recombination comprising; several restriction sites for cloning of recombinant proteins, a promoter (AOX1), termination sequences, selectable markers (zeocin), and α-factor secretion signal for expression in P. pastoris of antibodies (see pages 14-15 and 18). Moreover, one of ordinary skill in the art would have been motivated to construct vectors for cloning and methods of screening of transformed colonies for expression cassettes because Sambrook et al teach basic molecular biology methods for cloning and screening of transformed colonies and in view of the teachings of Sambrook one skilled in the art would also reasonably

conclude that when constructing recombinant vectors one would naturally analyze the DNA sequence for integrity and intactness and perform screening methods for obtaining the desired colonies. In addition, in view of the teachings of Horwitz et al one of ordinary skill in the art would know to use the methods of Western blot for detection of the expressed protein and test the antibody for antigen binding.

h. Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in producing a method for production of an antibody in P. pastoris because Horwitz et al teach the antibodies produced in yeast were secreted and functional by binding the target antigen (see abstract). In addition, one of ordinary skill in the art would have had a reasonable expectation of success in producing a method for production of an antibody in P. pastoris because Cregg et al teach the result of the engineered yeast is a yeast that is "easily scaled up from shake-flask to large-volume, high-density cultures with little change in the kinetics of product synthesis" (see abstract) Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in producing a method for production of an antibody in P. pastoris because the Invitrogen Catalog teach that the expression vector and P. pastoris makes "an ideal tool for laboratory research as well as industrial applications" (see page 14).

I. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

18. Claims 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horwitz et al and further in view of The 1997 Invitrogen Catalog.

a. The claims have been described supra. For this rejection, the term "system" in claim 20 is being interpreted as an expression vector and the P. pastoris yeast transformed for expression of heterologous proteins in P. pastoris.

b. Horwitz et al has been discussed supra. Horwitz et al does not teach an expression vector for production of antibodies in P. pastoris and transformants of P. pastoris. This deficiency is made up in the teachings of the 1997 Invitrogen Catalog.

c. The Invitrogen catalog has been described supra. The Invitrogen catalog also teaches the pA0815 vector. This vector was designed to generate multiple copies of the gene of interest in a single vector (See page 17).

d. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a recombinant P. pastoris vector containing dual expression cassettes, each carrying a cDNA copy of immunoglobulin light and heavy chain and P. pastoris transformed with cDNA encoding an antibody in view of Horwitz et al and the 1997 Invitrogen Catalog.

e. One of ordinary skill in the art would have been motivated to produce the claimed expression vector and P. pastoris transformed with expression cassettes for expression of an antibody because the Invitrogen Catalog teach a Pichia expression vector called pA0815 which "is specially designed to generate multiple copies of the gene of interest in a single vector" and

"increasing the number of copies of the gene of interest in a recombinant Pichia strain may increase protein expression levels" (see page 17). Thus, it would have been obvious to one of skill in the art to combine the DNA encoding for an antibody as taught by Horwitz et al in the expression vectors as taught by the Invitrogen catalog in order to produce high levels of expression of the antibody in P. pastoris.

f. Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in producing an expression vector and P. pastoris transformed with expression cassettes for expression of an antibody because Horwitz et al teach the antibodies produced in yeast were secreted and functional and bound the target antigen (see abstract). Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in producing an expression vector and P. pastoris transformed with expression cassettes for expression of an antibody because the Invitrogen Catalog teach that improved expression vectors and P. pastoris makes using these products faster and easier and is adaptable to industrial fermentation in fermentors as small as 1 liter and as large as 10,000 liters (see page 14).

g. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D., whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

21. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

JULIE BURKE
PRIMARY EXAMINER